Personalised adherence support for maintenance treatment of inflammatory bowel disease: A tailored digital intervention to change adherence-related beliefs and barriers

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Short title: Personalised digital IBD adherence intervention

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Abbreviations:

1 IBD: Inflammatory Bowel Disease

2 PPA: Perceptions and Practicalities Approach

3 BMQ: Beliefs about Medicines Questionnaire

Abstract

Background and Aaims: Interventions to improve adherence to medication may be more effective if tailored to the individual, addressing adherence-related beliefs about treatment and overcoming practical barriers to daily use. We evaluated whether an algorithm tailoring support to address perceptual and practical barriers to adherence reduced barriers and was acceptable to patients with IBD.

Methods: Participants with IBD, prescribed azathioprine and/or mesalazine were recruited via patient groups, social media and hospital clinics and allocated to Intervention or Control Groups. The online intervention comprised messages tailored to address beliefs about IBD and maintenance treatment and provide advice on overcoming practical difficulties with taking regular medication. The content was personalised to address specific perceptual and practical barriers identified by a pre-screening tool. Validated questionnaires assessed barriers to adherence and related secondary outcomes at baseline, 1e and 3 months of follow-up.

Results: A total of 329 participants were allocated to the Intervention [n=153] and Control [n=176] Groups; just under half [46.2%] completed follow-up. At one and three months the Intervention Group had significantly fewer concerns about IBD medication [p≤.01]; and, ~~at 3 months only~~at three months, fewer doubts about treatment necessity~~need~~, fewer reported practical barriers and ~~lower nonadherence~~higher reported adherence (p<.05]. Relative to controls at follow-up, the Intervention Group were more satisfied with information about IBD medicines, and viewed pharmaceuticals in general more positively. Questionnaires, interviews and intervention usage indicated the intervention was acceptable.

Conclusions: Personalised adherence support using a digital algorithm can help patients overcome perceptual barriers -(doubts about treatment necessity and medication concerns] and practical barriers to adherence.

Keywords: Medication nonadherence; inflammatory bowel disease; digital intervention, Necessity Concerns Framework, Persignia

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1. Introduction

Inflammatory bowel disease [IBD], comprising ulcerative colitis and Crohn's disease, is treated with maintenance drugs including mesalazine, thiopurines [e.g. azathioprine], anti-TNF therapies, and anti-integrins [e.g. vedolizumab] [1]. These drugs control flare-ups [2-4], avoid surgery, reduce colorectal cancer risk [1], and improve quality of life. However, an estimated 53-72% of people with IBD do not take their medication as prescribed, resulting in increased morbidity, healthcare costs, and decreased quality of life. [2,5-10]

Nonadherence to medication may be intentional and unintentional, arising from *motivation* and *ability*[11]. Motivation is influenced by ~~factors including~~ patients' perceptions and experience of IBD and maintenance treatment, and trust in the prescriber and prescription. Ability is influenced by internal factors (e.g. physical capability to administer maintenance treatment] and external factors (e.g. access to maintenance treatment] ~~factors~~. These principles are recognised in the Perceptions and Practicalities Approach (PAPA)[11] to supporting adherence, applied in NICE Medicines Adherence Guidelines[12] This approach suggests adherence support will be more effective if it addresses both the perceptions [e.g. beliefs about illness and treatment] and practicalities [e.g. capability and resources] affecting the individual's ability and motivation to adhere. The importance of addressing IBD patients' beliefs has been highlighted in ~~a~~ systematic reviews showing that judgements of personal need for maintenance medication [Necessity beliefs] and concerns about the adverse consequences of treatment were key determinants of nonadherence[13,14]. Horne's ~~The~~ Necessity-Concerns Framework states patients will be particularly motivated to take treatment when perceived personal need [Necessity beliefs] is high relative to concerns about potential ~~side~~ adverse effects ~~(Concerns beliefs)~~[15].

Medication beliefs [Necessity and Concerns] are influenced by perceptions of IBD and symptoms experiences[16]. Patients who ~~see~~ perceive a conceptual fit between their IBD (illness representations] and their maintenance treatment are more likely to think maintenance treatment is necessary. For many patients, taking medication does not 'make common-sense' when they feel well. Likewise, medication concerns ~~Concerns~~ may arise from perceiving symptoms as side effects. But, even patients who have not experienced side effects can harbour concerns e.g. about long-term effects, or dependence[16]. Such concerns ~~have been~~are often related to suspicions of pharmaceutical treatments and general background beliefs about

medicines [e.g. that they are intrinsically harmful] and to patients' perceived personal sensitivity to medication effects[16-18].

~~These findings suggest that~~We have developed a three stage Perceptions and Practicalities Approach to supporting adherence (PAPA]: 1] p~~P~~rovide a rationale for medication necessity so that patients perceive a 'common-sense' fit between IBD and treatment 2] elicit and address concerns about IBD medication and 3] address practical barriers to adherence. Studies in other long-term conditions have demonstrated the efficacy of this approach in improving adherence [e.g.[19-21]], but no interventions have incorporated this approach for IBD.

We report a 'proof of principle' study in which we examined a PAPA-based intervention in which support was tailored to address treatment necessity beliefs and concerns and help overcome practical barriers to adherence. We used an online platform to deliver the intervention because many patients with IBD access information online and because this support could be integrated with usual clinical care but accessed at patients' convenience.

Our aims were to: 1] develop the PAPA-based intervention and 2] e~~E~~valuate the intervention based on a] capacity to change perceptual and practical barriers to adherence; b] feasibility of delivering online; and c] acceptability to patients.

2. Methods

In line with the objectives, this study had two phases 1] intervention development and 2] intervention pilot.

2.1. Ethics and trial registration

The study received ethical approved from the NRES Committee London-Central. The trial protocol was registered with a clinical trial database http://clinicaltrials.gov/ (Identifier NCT01852097].

2.2 Phase 1: Intervention Development

We followed the recommendations of the MRC for complex intervention development, and considered research on the determinants of a behaviour and involving patients in the intervention design[22]. The adherence intervention was developed considering *content, context* and *channel* [*delivery vehicle*][23]

~~Regarding content,~~*Content:* our PAPA-based intervention applied National and European guidelines for IBD management[24-30], NICE adherence guidelines [12] and research about barriers to adherence in IBD[13,16]. We involved advisory panels of UK IBD patients and expert clinicians to ensure that the intervention was appropriate to the local healthcare context. To enable us to provide information about the medication participants were taking, we focused on two of the most common IBD maintenance medications available in practice at the time of the study design, azathioprine and mesalamine. The intervention addressed the 3-component PAPA model:

1]~~)~~ *Necessity*- a~~A~~ddressing doubts about need for medication

2]~~)~~ *Concerns*- a~~A~~ddressing concerns about potential adverse effects of medication

3]~~)~~ *Practical Barriers*- a~~A~~ddressing practical issues with taking medication in daily life

We also added an *IBD Library*- comprising general resources about living with IBD to complement the adherence support~~not tailored to address medication adherence directly~~.

Each of the three PAPA components was addressed using a number of Behaviour Change Techniques (BCTs][31], designed to modify behaviour regulatory processes. For example, to

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address treatment Necessity beliefs we used the BCTs 'Information on health consequences' and 'Credible Source', providing quotes from IBD experts to explain why patients need to take medication during both flare-ups and remission. Full details of the BCTs used in each part of the intervention and example content are presented in Supplement 1. Our communication strategy was informed by cognitive behavioural therapy and motivational interviewing, to ensure that the BCTs were delivered using language that would enhance awareness and intrinsic motivation.

~~Regarding~~ *Channel (delivery vehicle)*~~:~~ the content of the messages was personalised using the Persignia (working title] algorithm which tailors content to address specific perceptual and practical barriers identified by a pre-screening tool.

Context: ~~was used to~~we assessed whether the intervention content and channel would fit well with existing care pathways, we conducted three focus groups with 8 IBD patients. The Intervention Development Group (specialists in gastroenterology, clinical psychology, pharmacy, and health psychology] and three IBD patients undertook further usability testing. Further details and a sample page are presented in the Supplementary Material available as Supplementary data at *ECCO_JCC* online.

2.2. Phase 2: Intervention Pilot

2.3.1. Design

The pilot was a single-blinded, quasi-randomized trial of the online intervention comparing intervention and passive control [receiving standard care] groups. Patients completed the study measures three times: baseline [immediately prior to receiving the intervention link], at 1 month [30 days after starting the baseline measures, and at 3 months [90 days after starting the baseline measures]. Our primary outcomes were self-reported perceptual and practical barriers [BMQ Specific Concerns, BMQ Specific Necessity, and Practical Barriers]. We also tested whether the intervention had effects on a range of secondary outcomes: adherence, beliefs about medicines in general, perceived sensitivity to the effects of medicines, beliefs about IBD, satisfaction with information received about IBD medications, anxiety, depression, quality of life, reported disease activity, reported treatment seeking and reported burden of adverse effects to IBD maintenance treatment. We measured intervention usage

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statistics to assess feasibility. We used post-intervention questionnaires and interviews to gauge acceptability of the intervention.

2.3.2. Inclusion/Exclusion Criteria

We recruited people aged 18 years or older, who reported a diagnosis of IBD and a current prescription of azathioprine and/or mesalamine. We planned to exclude participants who did not report at least one perceptual or practical barrier [i.e. no concerns about their medication, no doubts about their need for medication and no practical barriers in the baseline questionnaire]. But all participants who entered the study reported at least one barrier.

2.3.3. Recruitment

Participants were recruited through Crohn's and Colitis UK's website, Facebook and Twitter accounts. We also placed leaflets and posters in IBD clinics at University College London Hospital and Brighton and Sussex University Hospitals NHS Trust. Potential participants followed a link to information about the study and an eligibility questionnaire. Eligible participants were then asked to provide informed consent. After the study commenced, we became concerned that the dropout rate was higher than expected. We introduced a prize draw for a £150 online gift voucher into which participants who completed all follow-ups would be entered.

2.3.4. Allocation

Participants were allocated to Intervention or Control Groups by a computer algorithm blind to their baseline characteristics. Due to an unanticipated technical issue this algorithm allocated slightly more participants to the Control Group than the Intervention Group as the study progressed[a], and so although blind, was not fully randomized. As a result of this technical issue, 7 participants who resubmitted their baseline questionnaires [we suspect by

[a] We planned to stratify participants by medication (azathioprine/mesalamine/both) and randomize using a computer generated random number sequence. To ensure equal group numbers, this was operationalized using a minimization algorithm; with the first participant in each strata randomized and subsequent participants assigned to the group with fewest participants for their medication. Due to an unanticipated feature of the platform, participants had new random allocation values encoded when completing follow-up questionnaires. These new allocation values, rather than original allocations, were used to randomize new participants. More Intervention Group participants dropped-out, so, as the study progressed these participants had an allocation value frozen at Intervention, meaning subsequent allocations were more likely to be to the Control Group. Thus we did not randomize. However, the algorithm had no effect on the intervention content presented to participants.

hitting refresh mid-submission] were allocated twice at baseline and recorded on our system as allocated to both the Control and Intervention Groups. To avoid potentially cross-contaminated participants, we excluded these from the analyses below.

2.3.5 Measures

Participants received the same questionnaire package at baseline, 1 and 3 months, which took approximately 25 minutes to complete. It ~~included~~ comprised the following measures:

Beliefs about Medicine Questionnaire [BMQ] The BMQ is a validated questionnaire tool[32] with two parts, the BMQ-Specific, assessing patients' evaluations of a particular medicine for a particular condition, in this case maintenance treatment for IBD, and the BMQ-General, assessing patients' evaluations of pharmaceuticals as a class of treatments.

There are two BMQ Specific scales: ~~,~~ BMQ Necessity [5-items], which assesses perceptions of need for IBD medication [e.g. '*My life would be impossible without mesalazine/azathioprine'*] and BMQ Concerns [6-items], which assesses ~~beliefs~~ concerns about potential adverse effects of IBD medication [e.g. *'Having to take mesalazine/azathioprine worries me'*]. Participants either completed a BMQ Specific for azathioprine [AZA], or mesalamine/ [MES] or both medicines, depending on whether they were taking AZA, MES or both. Where participants completed both scales, we took their highest BMQ Concerns score and their lowest BMQ Necessity score on the basis that these scores would be indicative of barriers to adherence. A Necessity-Concerns Differential score [BMQ NCD], indexing patients' overall evaluation of personal necessity relative to ~~concerns'~~concerns ~~of~~ about their IBD treatment was calculated by subtracting BMQ Concerns scores from BMQ Necessity scores[16].

The BMQ General comprised three scales evaluating perceptions of whether pharmaceutical medications are generally harmful [General Harm; 5 items; e.g. '*M~~m~~edicines do more harm than good'*], overused and overprescribed by medical practitioners [General Overuse; 3 items], or beneficial to patients and society [General Benefit; 4 items]. All items are assessed on Likert type scales anchored from 1=strongly agree to 5=strongly disagree. The measure has been applied in IBD research [16]. In the current sample, all BMQ scales had good internal reliability at baseline [Cronbach's αs=0.74-0.91].

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Perceived Sensitivity to Medicines Scale [PSM]. The validated PSM[33] assesses perceptions of their personal sensitivity to the positive and negative effects of medicines. Participants indicate their agreement with 5 items on the same Likert-type scale as used in the BMQ. The scale had good internal reliability at baseline in the current study [Cronbach's α=0.90].

Perceptual Barriers Profiler. In addition to the full BMQ, an IBD BMQ Specific Profiler was used to identify specific doubts and concerns about each IBD treatment. Participants were asked indicate whether they had doubts about treatment need or concerns about adverse effects by responding simply 'yes' or 'no' to doubts or concerns based on the BMQ Specific items [17 items for AZA and 17 items for MES].

*Practical Barriers Profiler***.** A scale to profile participants' experience of practical barriers to taking medication was created by asking participants to respond 'yes' or 'no' to 10 practical issues that they might experience when taking their IBD medication. For example 'I find it difficult to remember to take my medicines when my daily routine changes'. We calculated the total number of practical barriers endorsed [possible range 0-10] as a 'Practical Barriers' score.

The Perceptual and Practical Barriers Profilers were used as part of the Persignia system to tailor the intervention content presented to participants. Participants who reported any Necessity Barriers received all the Necessity pages. Participants who reported Concerns or Practical Barriers received specific pages tailored to their individual barriers to reduce burden and ensure that barriers were not suggested to patients. For example, only participants who reported a Concern about long-term effects of treatment received information about cancer risks. All participants received access to the IBD Library.

Medication Adherence Report Scale [MARS] The MARS is a validated measure[34,35] of self-reported adherence to medication. The MARS ~~scale~~ has been extensively used to measure self-report of the frequency of nonadherent behaviours [e.g. 'I forget to take azathioprine'] in a variety of illness populations including IBD[14,16,34,36-39]. The MARS attempts to diminish the social pressure on patients to under-report non-adherence by phrasing adherence questions in a non-threatening manner. In the current study we used a 6-item version scored from 1=very often to 5=never resulting in a possible range of total scores of 6-30, 30 indicating the highest self-reported adherence. Participants completed separate scales for AZA, MES or both. For

the combined analysis, we used the lowest reported score. The scale had good baseline internal reliability for both MES [Cronbach's α=0.80] and AZA [Cronbach's α=0.81].

~~Using the~~ *Adherence Visual Analogue Scale [VAS].* Patients reported an estimate of the percentage of their AZA and/or MES medication taken over the last week on a scale from 0-100%.

~~The~~ *Brief Illness Perception Questionnaire [IPQ]* [40] is an assessment of cognitive and emotional representations of illness, on eight dimensions. Patients rated their perceptions of the following aspects of their IBD: its impact on their lives [consequences], chronicity [timeline], whether they could it [personal control], whether their treatment could control it [treatment control], severity of symptoms [identity], concern about their symptoms [concern], understanding of their IBD [understanding], and distressed about their IBD [emotional response]. Patients responded to each item on a scale of 0-10.

~~The~~ *Satisfaction with Information about Medicines Scale [SIMS]* ~~-~~ assesses how satisfied patients are with the information they have received about their medication[41]. It has two subscales: SIMS Action and Usage [SIMS-AU], measuring satisfaction with information about the action and usage of IBD medication and SIMS Potential Problems [SIMS-PP] measuring satisfaction with information about the potential problems that might arise while taking IBD medication. In the current study, both subscales had good internal reliability Cronbach's αs SIMS AU=0.81, SIMS PP=0.88].

~~The~~ *Hospital Anxiety and Depression Scale [HADS]* measures current symptoms of anxiety and depression on two 7-item scales. It has good reliability and validity across diseases[42]. In the current sample both scales had good internal reliability at baseline [both Cronbach's αs =0.83]. We categorised patients as being at risk for clinically significant anxiety and depression if their total score [possible range 0-21] on either subscale was above 10.

~~The~~ *Short Inflammatory Bowel Disease Questionnaire [SIBDQ]* ~~. The SIBDQ~~ measures quality of life in IBD and has been found to be valid, reliable and sensitive to clinical changes[43] [Cronbach's α=0.87 in current study]. The scale has 10 items that are summed to form a total score [range 10-70] with higher scores indicative of better health.

Demographic and clinical information. Participants reported demographic factors: their date of birth, gender, marital status, level of education, and ethnicity. They also reported clinical

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information: age when diagnosed with IBD, whether they were currently in remission or having a flare-up, number of flare-ups experienced in the last 3 months, medications prescribed for IBD, and number of consultations for IBD [planned and unplanned] with healthcare professionals in the last 3 months.

2.3. Acceptability and Usage Assessments

We conducted quantitative and qualitative assessments of the acceptability of the intervention. We also assessed intervention usage by evaluating which participants had logged in, for how long, and to which sections of the website.

Quantitative Assessment- Acceptability Questionnaire. After completing, the final 3-month follow-up participants in the Intervention Group were automatically emailed a link to a brief, final questionnaire evaluating the intervention. This included 17 statements about the functionality, usefulness and trustworthiness of the website e.g. 'I think the information on this website was not convincing', which participants rated their agreement with on a 5-point Likert-type scale [1=strongly agree, 5=strongly disagree].

Qualitative Assessment-Acceptability Interviews. When giving informed consent, participants were asked if they would be willing to be contacted for a follow-up telephone interview. After recruitment and follow-up was complete, we contacted participants who had expressed interest in this who were in the Intervention Group. We purposively sampled 6 male and female participants who had and hadn't used the intervention. Two research assistants trained in qualitative methods conducted telephone interviews using a semi-structured interview schedule to explore experiences of the intervention. The interviews were transcribed and themes and quotes from the interviews are used below to provide context to the quantitative data collected.

Intervention Usage Statistics. The platform automatically recorded the time each page of the Intervention site was accessed. Using this information, we were able to calculate the total time spent accessing the website by each participant and check when the intervention content was accessed over the follow-up period [i.e. total number of visits to the intervention, total time spent across intervention, date of first access].

2.4. Statistical Analysis and Sample Size Calculation

We determined the sample size needed to obtain 80% power to detect a statistically significant [p≤.05] medium-sized difference [Cohen's d=0.5] in beliefs between Control and Intervention Groups at follow-up using the statistical package G*Power 3.1.3 [® Dusseldorf], based on effect sizes for other online interventions [44]. We estimated 128 participants [64 per group] were necessary, rising to 214 assuming a 40% drop-out rate.

Statistical analysis was undertaken using SPSS 21 [®, IBM]. We used intention-to-treat analysis [i.e. without excluding participants who did not access the intervention] to assess the unbiased effect of the intervention. We tested for normality of our variables and used means and standard deviations to describe normally distributed variables, and medians and interquartile ranges to describe skewed variables. At baseline, 1 month and 3 months follow-up we tested for between-group differences in each variable using t-tests with Levene's adjustment for unequal distributions or Mann-Whitney U-tests as appropriate.

3. Results

3.1. Recruitment and Retention

The screening questionnaire was completed by 1267 potential participants, 1115 of whom met the eligibility criteria, 381 participants consented to take part in the study and started the baseline questionnaire. See Figure 1 for recruitment and retention. Over 300 patients [329] were allocated to intervention or control. At 3 months follow-up, just 46.2% of participants were retained in the study.

3.2. Sample demographics

As shown in Table 1, the ~~The~~ sample was 72.8% female [n=238]. Participants were aged between 18.5 years and 73.0 years, the median age was 36.3 years. The sample was 89.3% White British [n=293]. One hundred and fifty-six participants had obtained a degree or higher degree [47.7%].

3.3 Baseline clinical status

At baseline, 54.3% of participants reported that they were currently experiencing a mild to moderate flare-up [n=117] and 35.7% were in remission [n=117] and the remainder reported a current severe flare-up [n=33, 10.1%]. The median number of flare-ups reported by participants in the previous 3 months was 1 [range 0-31], with 75.2% of participants reporting at least one recent flare-up. Healthcare seeking for IBD was not high; most participants reported 1 or fewer GP, consultant, nurse, telephone helpline, or pharmacist contacts. 72.9% of participants were taking mesalamine and 54.7% were taking azathioprine. See Table 2 for statistics.

The mean HADS anxiety score was 9.9 [SD=4.3]. The mean HADS depression score was 7.5 [SD=2.2]. Overall, 133 participants [41.8%] scored above 10 for HADS anxiety, and 70 [21.5%] scored above 10 for HADS depression, indicating risk of clinical significance.

3.4. Primary outcome: Perceptual and practical barriers to adherence

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Participants reported both perceptual and practical barriers to taking their IBD medication at baseline. On the profiling scale 90.8% [n=267] of participants reported at least one concern about their medication, 95.4% [n=312] had at least one doubt about whether their IBD

medication was needed, and 89.9% [n=295] had at least one practical barrier to taking their IBD medication.

Pre-intervention, participants in the Intervention and Control Groups reported similar levels of concerns about their medication [BMQ Specific Concerns], and doubts about necessity [BMQ Specific Necessity]. We split participants into those who reported high and low concerns and necessity beliefs using the midpoint of the scales [as per [16]]. At baseline, 30.5% [n=99] of participants reported significant doubts about their need for their IBD medication [low BMQ Specific Necessity], and 43.3% [n=141] reported high concerns about the potential adverse effects of their IBD medication [high BMQ Specific Concerns]. Descriptive statistics for BMQ Specific Necessity, BMQ Specific Concerns, and the difference between these two scores [Necessity Concerns Differential: BMQ NCD] are presented in Table 3.

3.5. Specific beliefs at follow-up

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At both 1 and 3 months follow-up, the Intervention Group had a higher BMQ NCD score, indicating that their belief in their personal need for medication tended to outweigh their concerns to a greater extent than it did for the Control Group, and this was statistically significant at 3 months. They also expressed statistically significantly fewer doubts about their personal need for IBD medication at 3 months, and fewer concerns about the potential adverse effects of IBD medication at 1 and 3 months [see Table 3 and Figure 2].

3.6. Practical barriers to taking medication at follow-up

Intervention Group participants reported fewer practical barriers to taking medication at both follow-up time points, but this was only statistically significant at 3 months [see Table 3].

3.7. Secondary Outcomes

See Tables 4 for descriptive statistics and between-group comparisons.

3.7.1 Adherence

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Reported adherence to medication was high; at baseline the median MARS score was 28 [range 10-30] and the median VAS adherence was 100% [range 0-100]. Likewise at both follow-ups, the median VAS score was 100% in both groups for both medications. Due to highly skewed data, we used non-parametric tests, to assess whether mean ranks of adherence scores were different between the Intervention and Control groups over follow-up. At 1- and

3-months post-intervention the Intervention Group had higher VAS adherence than Controls, higher adherence to mesalamine alone at 1 month on the VAS, and higher adherence to azathioprine on both VAS and MARS at 3 months. There were no statistically significant differences between groups for MARS adherence to mesalamine.

3.7.2. Satisfaction with information about IBD medication

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At baseline participants reported that they were satisfied with a mean of 7.01 SIMS items about Action and Usage [of a total of 9] and 4.82 SIMS items about the Potential Problems associated with their medication [of a total of 8]. There were no differences between the Intervention and Control Groups in terms of satisfaction with information at baseline.

Intervention Group participants were more satisfied with the information they had received about the potential problems associated with IBD medication [SIMS PP] than Controls at both follow-up points [$p < .05$]. Intervention participants were also more satisfied with the information they had received about the action and usage of medication [SIMS AU] at both follow-up points, but this was only statistically significant at 1 month [$p < .05$].

3.7.3. General beliefs about pharmaceuticals as a class of treatment

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The groups were not statistically significantly different on general beliefs about pharmaceutical medication: BMQ General Harm, BMQ General Overuse, BMQ General Benefit and Perceived Sensitivity to Medicines at baseline. The Intervention Group were less likely than Controls to believe that pharmaceutical medication is generally overused [BMQ General Overuse] and harmful [BMQ General Harm] at both 1 month and 3 months follow-up [$p< .05$]. There were no statistically significant effects at either time on the belief that medications are generally beneficial [BMQ General Benefit] or on patients' perceptions of their own sensitivity to the effects of medications [PSM].

3.7.4. Illness beliefs

Participants' scores on the Brief IPQ at baseline indicated that participants felt their IBD was fairly severe, chronic, distressing and concerning but relatively well understood [see Supplementary material for individual item scores. There was no overall difference in baseline brief IPQ scores but a small statistically significant difference between groups at baseline in treatment control beliefs; patients in the Intervention Group reported slightly more agreement that their treatment can control their IBD than participants in the Control Group.

Participants in the Intervention Group had viewed their IBD more positively than Controls at 1 and 3 months although this was only statistically significant at 1 month [see Table 4].

3.7.5. Quality of life, Anxiety and Depression

Participants in the Intervention Group reported less anxiety and depression than controls [HADS Anxiety and HADS Depression scales] and higher IBD-related quality of life [SIBDQ] at both follow-up points. However, the differences between groups were only statistically significant for anxiety and depression at the 3-month follow-up. See Table 4 for means, medians and t-tests.

3.8. Acceptability Questionnaire and Interviews

Analysis of the acceptability interviews is presented in the Appendix. Thirty-two participants in the Intervention Group filled in the acceptability questionnaire. The website was rated as 'easy to understand' by 100% [n=32] of participants and 'easy to navigate' by 93.3% [n=28] of participants. A small number of participants indicated they found the website slow to load [n=4, 13.3%] and unattractive [n=6, 20.0%]. Most participants disagreed or strongly disagreed that the website 'took too long' 84.4% [n=27], was 'not relevant to me' 75.0% [n=24], 'not believable' 87.5% [n=28], and 'not convincing' 84.4% [n=27], indicating positive views of the website. Likewise, 56.3% [n=18] agreed or strongly agreed that the cartoons were helpful, 62.5% [n=20] were happy with the number of questions on the website, and 59.4% [n=19] thought the website had made them think. Perceptions of the intervention team were positive; the majority of the respondents rated the team as 'credible' [86.7% n=26], 'trustworthy' [83.3%, n=25], 'dependable' [76.7%, n=23], 'reliable' [73.3%, n=22], and 'reputable' [83.3%, n=25].

3.9. Intervention Usage

The intervention was used by 73.2% [n=112] of the Intervention Group. Of participants who logged on to the intervention, the maximum number of sessions was 5 and slightly over half of participants [54.9%, n=84] logged on once with the remaining participants using the intervention on multiple occasions. The total time spent on the website varied between <0.01 seconds and 73 minutes, [median = 9.36 minutes]. Participants accessed a median of 22 pages [range 1-124].

Forty-one participants [26.8%] in the Intervention Group never logged on to the intervention. There were no differences between participants who logged on to the intervention and those who did not in terms of demographic variables [age, gender, ethnicity or education level], baseline specific beliefs about medication for IBD [Specific Necessity and Concerns], baseline general beliefs about medications [Harm, Overuse, Benefits], perceived personal sensitivity to medicines, illness beliefs [IPQ], anxiety, depression or self-reported adherence [all $p > .05$].

The most frequently visited area of the website was the Practical Barriers section, which 75.9% [n=85] of participants used. The Concerns section was accessed by 56.3% [n=63], the Necessity sections by 45.5% [n=51] and the IBD library section by 34.8% [n=39].

4. Discussion

This is the first study to evaluate an intervention to change adherence-related beliefs about maintenance treatment for IBD. We found a clear need for the intervention; all potential participants reported some doubt about the personal necessity of medication, concern about medicines, or practical barrier to adherence. There was evidence the intervention effectively addressed these barriers.

Perceptual and practical barriers have been associated with adherence in IBD [13,16,45]. From equivalence at baseline, intervention participants had statistically significantly stronger beliefs in the necessity of their medication at 3-months follow up relative to the Control group. This was achieved by providing patients with a common-sense rationale for treatment and using the Persignia algorithm [working title]. The intervention also reduced concerns about medication over time relative to the Control Group.

There were other indicators of efficacy on secondary outcomes. Intervention Group participants reported more satisfaction with information about IBD medication, more positive beliefs about medications in general, and more positive views of IBD than the Control Group at follow-up. This suggests that addressing barriers to adherence may affect multiple variables relevant to IBD self-management. The acceptability questionnaire recorded largely positive views of the intervention. Participant interviews indicated the content was useful and trustworthy, and suggested areas for further development including technical issues relating to the web-based delivery channel. Intervention usage statistics indicated most participants spent less than 15 minutes using the intervention. The online PAPA-based intervention has the capacity to modify adherence barriers, is likely to be acceptable to patients and feasible to deliver.

The intervention was less robust on other variables. Relative to Controls, Intervention Group participants reported fewer practical barriers at 1 and 3 months follow-up, this difference was only statistically significant at 3 months. The more modest change in practical barriers could indicate a need for face-to-face or other support to address practical factors such as difficulty in obtaining prescriptions or regimen complexity. Self-reported adherence was higher in the Intervention Group at 1 month and 3 months follow-up but this was only statistically significant for the VAS measure at 3 months. These differences are small and ~~unlikely~~ may not ~~to~~ affect clinical outcomes in the short term. However, over time, not addressing barriers

to adherence may increase vulnerability to nonadherence and subsequently flare-ups and hospitalisations. We found higher levels of reported adherence than previously reported in IBD[2,5,10], perhaps indicating that participants were more highly engaged with their care than is typical or that they under-reported nonadherence which may have placed a ceiling effect on improvements in adherence.

Usage statistics indicated that patients varied in their use of the intervention, with some using the intervention for a single short visit and others returning several times to the resources. Overall, the median intervention usage time was under 10 minutes, indicating that it can be considered to be low intensity relative to traditional face-to-face interventions that require a series of appointments. Post-intervention questionnaires indicated that the intervention content, website function and perceptions of the intervention source were largely positive. Most participants who completed the feedback scale rated the website content as useful, the research team as reliable and expert, and the loading of the website was not too slow. It appears therefore that the intervention was largely acceptable to participants.

4.1. Limitations

Although our findings are promising and provide 'proof of principle' that tailored messages can change adherence-related perceptual dn practical barriers, the efficacy of the approach needs to be further tested in a full-scale RCT. Several limitations of trial design and conduct mean that the current results do not represent a full test: allocation was blind but not fully randomised, high dropout rates, and the monetary stimulus may also have biased the results of this pilot[46]. Our attrition rate is typical of internet-based trials. Perhaps the initial decision to participate online requires less engagement, meaning participants are more prone to drop-out. Internet-based trials are more 'pragmatic' and typical of practice than clinical trials e.g. our high drop-out rate may parallel poorer attendance at follow-up appointments when patients are recovered, however we cannot evaluate this using our data. We only have self-reported prescriptions, clinical and adherence data, up to 3 months follow-up, limiting recommendations regarding use of the intervention in practice[47]. The study was not powered to determine effects on flare-ups or healthcare seeking. Finally, our participants may represent a subset of relatively highly engaged IBD patients and therefore these findings may not generalise.

4.2. Implications for clinicians and policymakers

Despite these limitations, these findings suggest that management of IBD may be improved by providing online support to patients to address their personal barriers to adherence. Our results indicate that directly addressing patients' adherence-related beliefs about treatment [necessity and concerns] is possible, in a brief, low-impact digital intervention and that this could impact positively on self-management to augment clinical care. Online resources providing such personalised information may therefore be a useful addition to existing models of care. This could be explored further in different healthcare settings [e.g. resource limited settings,] and for different treatment regimens [e.g. steroids and biologics]. While we focused on mesalazine and azathioprine, patients also have concerns about new biologic therapies, suggesting a similar intervention may support adherence to these drugs[48,49].

5. Conclusion

A PAPA-based intervention changed adherence-related medication necessity beliefs and concerns and practical barriers. Online interventions providing tailored information addressing barriers to medication taking may be an acceptable and feasible tool for supporting IBD patients to adhere to treatment. Potentially, this intervention may reduce flare-ups, hospital admissions and other clinical indicators, however full trials are needed to evaluate this. These findings suggest that a brief, online PAPA-based intervention has the capacity to support adherence, is acceptable and feasible.

Acknowledgements

We are grateful to Crohn's and Colitis UK for their support of this project. We would also like to thank Elizabeth Poliquin, Kathryn King, Paulina Bondaronek, Federica Picarello, Sarah-Jane Besser, and Helen Barker for their assistance with recruitment of participants and follow-up, and with conducting and transcribing interviews. We are grateful to Spoonful of Sugar Ltd [a UCL Business spin-out Company] for allowing us to use the Persignia™ System [content management and algorithm]. We also thank Chris Dickinson [Spoonful of Sugar], and White October and the staff at LifeGuide for their support with the screening questionnaire. Last, and by no means least, we would like to thank the members of CCUK who supported recruitment for this project, provided input to the development of the intervention and participated in the study.

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Guarantor of this article: Prof Robert Horne

Author contributions

SC: Assisted with recruitment and follow-up, collecting qualitative data and website usage data, conducted the analysis, and drafted the manuscript.

AS: Contributed to all aspects of study including intervention design, recruitment, data analysis and the draft manuscript.

AS-CJ: Clinical Pharmacist involved in the study design, development of the medicines information and review of protocol and manuscript

AF: Clinical gastroenterologist closely involved in the design of the study, review of all versions of the protocol and the permissions' process, with surveillance of data collection and analysis, and direct involvement in the writing and editing of the subsequent manuscript.

AC: Assisted with the development of the online material, website pages and linkage to behaviour change techniques and cognitive behavioural therapy/motivational interviewing. She assisted with the initial intervention protocol and provided feedback on the draft manuscript.

RH: Conceptualised the study and contributed to all aspects of study including intervention design, recruitment, data analysis and the draft manuscript.

All authors approve this final draft for submission.

Financial support: This study was funded by a 'Living with IBD' grant from Crohn's and Colitis UK (CCUK). The work was conducted independently of CCUK.

Potential competing interests:

AF has undertaken speaker engagements for Dr Falk Pharma and in the more distant past for other pharmaceutical companies who produce mesalazine and azathioprine, but has no other competing interests to declare.

ASCJ has undertaken speaker engagements for Ferring Pharmaceutical Ltd and Actavis in the past but not for the last two years. No other competing interest to declare.

All other authors have no competing interests to declare.

Figure Legends

Figure 1: Participant flow chart

Note: AZA = participants taking azathioprine, MES = participants taking mesalamine, AZA+MES = participants taking both azathioprine and mesalamine.

*371 started baseline measures but of these, 42 participants dropped out before completing baseline.

Figure 2: Mean BMQ Necessity and Concern beliefs at baseline and follow-up

Note: BMQ = Beliefs about Medicines Questionnaire Necessity and Concerns scores

Tables

Table 1: Sample Demographics

Note: IG=Intervention Group, CG=Control Group

	IG n=153	CG n=176
Gender: n(%) female	111 (72.5%)	127 (72.2%)
Ethnicity: n(%) White British	137 (89.5%)	156 (88.6%)
Age in years: Median [IQR]	36.0 [27.9-47.1]	36.8 [28.7-45.1]
Education: n(%) with degree/higher degree	76 (49.7%)	80 (46.0%)
Marital status: n(%) married/civil partnership/cohabiting	94 (61.4%)	100 (56.8%)

Table 2: Clinical descriptive statistics

Note: IG=Intervention Group, CG=Control Group.

	IG n=153	CG n=176
Current reported IBD status n(%)		
… in remission	57 (37.3%)	60 (34.3%)
…mild to moderate flare-up	82 (53.6%)	96 (54.9%)
…severe flare-up	14 (9.2%)	19 (10.8%)
Last 3 months, number of... median[IQR]		
flare-ups	1 [0-2]	1 [1-2]
flare-ups leading to change in treatment	0 [0-1]	0 [0-1]
face-to-face GP consultations	1 [0-2]	1 [0-3]
planned face-to-face GP consultations	0 [0-1]	0 [0-1]
face-to-face IBD consultant consultations	1 [0-2]	1 [0-2]
planned face-to-face IBD consultant consultations	1 [0-1]	1 [0-1]
face-to-face IBD nurse consultations	0 [0-1]	0 [0-0]
telephone/email contacts with IBD nurse	0 [0-3]	0 [0-3]
IBD nurse helpline contacts	0 [0-1]	0 [0-1]
face-to-face consultations with hospital/retail pharmacist	0 [0-1]	0 [0-1]
Current prescription n(%)		
Mesalamine	112 (73.2%)	128 (72.7%)
Azathioprine	82 (53.6%)	98 (55.7%)
Mercaptopurine	3 (2.0%)	10 (5.7%)
Prednisolone	40 (26.1%)	44 (25.0%)
Budesonide	8 (5.2%)	10 (5.7%)
Hydrocortisone	3 (2.0%)	10 (5.7%)
Infliximab	10 (6.5%)	13 (7.4%)
Adalimumab	14 (9.2%)	11 (6.3%)
Methotrexate	4 (2.6%)	1 (0.6%)

Table 3: Means, standard deviations and group comparisons (t-tests) for primary outcomes

Note: IG=Intervention Group, CG=Control Group, BMQ = Beliefs about Medicines Questionnaire, NCD = Necessity Concerns Differential.

	Baseline			1 month			3 months		
	IG n=153 **m (SD)**	**CG** n=176 **m (SD)**	**p**	**IG** n=115 **m (SD)**	**CG** n=154 **m (SD)**	**p**	**IG** n=44 **m (SD)**	**CG** n=108 **m (SD)**	**p**
BMQ Concerns	2.86 (0.77)	2.94 (0.80)	.39	2.61 (0.86)	2.90 (0.84)	**.01**	2.52 (0.77)	2.98 (0.79)	**<.01**
BMQ Necessity	3.26 (0.92)	3.21 (0.91)	.57	3.20 (1.05)	3.20 (0.93)	.96	3.39 (1.01)	2.94 (1.03)	**.02**
BMQ NCD	0.40 (1.11)	0.26 (1.12)	.27	0.59 (1.21)	0.30 (1.20)	.07	0.87 (1.24)	-0.03 (1.18)	**<.001**
Practical Barriers	3.58 (2.67)	3.50 (2.49)	.78	3.19 (3.15)	3.50 (2.80)	.43	2.18 (2.29)	3.25 (2.77)	**.03**

Table 4: Descriptive statistics m(SD) or median [interquartile range] and group comparisons for secondary outcomes

Notes: All comparisons t tests except for MARS and VASA where Mann-Whitney U results reported; IG=Intervention Group, CG=Control Group, MARS = Medication Adherence Report Scale, VASA = Adherence VAS, BMQ = Beliefs about Medicines Questionnaire, PSM = Perceived Sensitivity to Medicines Scale, HADS = Hospital Anxiety and Depression Scale, SIBDQ = Short Inflammatory Bowel Disease Questionnaire, SIMS AU = Satisfaction with Information about Medicines Action and Usage Subscale, SIMS PP = Satisfaction with Information about Medicines Potential Problems Subscale. Brief Illness Perception Questionnaire results in Supplementary Content.

	Baseline			**1 month**			**3 months**		
	IG n=153	**CG** n=176	**p**	**IG** n=115	**CG** n=154	**p**	**IG** n=44	**CG** n=108	**p**
MARS	28 [24-30]	28 [25-30]	.97	29 [25-30]	28 [25-30]	.55	29 [27.3-30]	28.5 [25-30]	.10
VASA	100 [90-100]	100 [90-100]	.57	100 [90-100]	100 [90-100]	.23	100 [90-100]	100 [90-100]	**.03**
BMQ Harm	2.22 (0.68)	2.23 (0.66)	.92	2.11 (0.79)	2.30 (0.66)	**.05**	1.99 (0.57)	2.26 (0.61)	**.02**
BMQ Overuse	2.74 (0.88)	2.87 (0.86)	.19	2.67 (0.95)	3.03 (0.88)	**<.01**	2.62 (0.69)	3.07 (0.90)	**<.01**
BMQ Benefit	3.97 (0.54)	3.89 (0.64)	.25	3.97 (0.53)	3.91 (0.53)	.34	3.93 (0.48)	3.88 (0.46)	.63
PSM	2.80 (0.94)	2.83 (0.92)	.73	2.74 (1.03)	2.84 (0.91)	.40	2.86 (1.06)	2.82 (0.91)	.85
HADS Anxiety	9.79 (4.41)	9.97 (4.18)	.71	8.61 (4.91)	9.63 (4.52)	.11	7.26 (4.87)	9.53 (3.99)	**<.01**
HADS Depression	7.47 (4.23)	7.57 (4.21)	.84	6.70 (4.71)	7.69 (4.52)	.11	5.74 (4.10)	7.08 (4.09)	**<.01**
SIBDQ	38.01 (11.22)	36.91 (12.46)	.41	41.77 (13.19)	39.60 (13.47)	.23	44.15 (12.59)	41.11 (11.87)	.18
SIMS AU	7.08 (2.28)	6.94 (2.11)	.58	7.90 (2.19)	7.27 (2.27)	**.03**	7.52 (2.35)	8.27 (2.32)	.09
SIMS PP	4.97 (2.54)	4.69 (2.49)	.32	5.79 (2.51)	5.02 (2.61)	**.03**	7.04 (2.23)	5.27 (2.67)	**<.001**
Brief IPQ	55.19 (7.38)	55.27 (8.15)	.92	53.16 (7.51)	55.17 (7.68)	**.04**	52.65 (8.78)	54.76 (8.58)	.20